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PATHOGENICITY OF NEWCASTLE DISEASE FOR MAN

Zoonofilassi (Veterinary Prophylaxis),
Vol 16, 1961, pages 687-700.

by B. Alby

[Note]: At the time of publication B. Alby was a guest of the University of Messina's Institute for Veterinary Infectious Diseases, Prophylaxis and Control, whose director was A. Bonaduce.

Summary: The author examines the Newcastle disease virus's pathogenic action on man.

It is already known that Newcastle disease virus can bring harm to man and that this can take place in different ways. One should rather mention the fact that medical literature on the subject is receiving an increased number of interesting reports on the subject, wherein the pathogenic action of the disease appears more and more to be of a proteinic type, even if its effects fortunately do not give rise to worry considering at least the relative benignancy of the cases hitherto described.

Without taking into account this virus's affinity to influenza virus shown by Burnet (14) in 1943 and later by Carlinfanti (16), it would seem that it would be able to produce a set of influenzal symptoms in man (Howitt, et al (32), etc.). When a study was started on the avian pneumoencephalitis virus in Montgomery, Alabama, laboratories, a virus which as has been shown by Beach (4) is none other than that of Newcastle disease, six employees came down with an illness similar to influenza. The sera of these persons showed a high level of antibodies specific for Newcastle disease virus. Recently, Negri, et al (56) have retransmitted Newcastle disease to chickens by inoculating them with the blood of an eleven-year-old girl who showed symptoms of an influenzal form: moderate fever (37.5°C.), chills, headache and intense intolerance of light.

The Newcastle disease virus may be met with in simple, atypical pneumonia, as has been noted by Atanasiu (2), and also can be responsible for gastrointestinal disturbances (McGough (50), etc.).

Positive serological reactions to Newcastle disease virus have been found in patients affected by acquired hemolytic anemia of unascertainable origin. Eyquem, et al (25), in investigations of the hemagglutination inhibiting action of sera taken from patients affected by various hemolytic

syndromes against Newcastle disease virus, found that seven sera out of 129 showed inhibiting action. Nevertheless, this inhibition was sometimes difficult to bring out due to the existence of a chicken anti-red cell agglutinin. Once this agglutinin was absorbed using freshly obtained chicken red cells it was found that three sera showed a considerably high inhibiting power (1:1,200), but only one of these sera came from a subject with hemolytic anemia with hemolysin. The other two sera came from a patient with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli disease) and another patient with spherocytic, congenital anemia. In one case of acquired hemolytic anemia involving a boy, the serum inhibited up to 1:160.

Sera taken from 34 cases of acquired hemolytic anemia showed no inhibiting action.

All the other syndromes were of patients suffering from various hemolytic syndromes: Marchiafava-Micheli disease, Lederer's anemia, hemoglobinuric biliary purpura, syphilitic anemia, paroxysmal anemia a frigore, anemia with positive Hirst reaction, hemolytic syndrome associated with Hodgkin's disease, myeloid and lymphoid leukemia.

The authors have concluded from these first results that Newcastle disease virus apparently cannot be held to be any important cause of acquired hemolytic anemias in man.

During the course of experiments carried out in the Caracas Veterinary Research Institute, one person was infected with Newcastle disease due to accidental ingestion., showing signs of illness (described in the Bulletin of the Institute of Veterinary Research, December 1953), and consisting in development of parotitis on one side. Newcastle disease virus was re-isolated from the patient and identified as such (62).

Epidemic hemorrhagic fever in man has been attributed to Newcastle disease virus. Garcia (28) observed 11 cases of epidemic hemorrhagic fever in Manila, two of which proved fatal.

The clinical course of these two cases was identical. Hypotensive condition, oliguria, high fever, marked redness of the eyes, face and neck, petechiae, nosebleed, bleeding gums, blood-colored extremities, pronounced headache and convulsive manifestations.

Mice, rats, guinea pigs and rabbits inoculated with blood from the extremities of such patients showed no signs of any symptoms, while chickens died 11 days after such inoculation, with post mortem findings indicating Newcastle disease.

Chicken eggs inoculated with the blood of these animals died, and their amniotic and allantoic fluids had the property of agglutinating the blood corpuscles.

On the basis of the studies carried out, the author concludes that the two cases are certainly to be attributed to Newcastle disease.

Newcastle disease virus was held responsible for symptoms of nervous system disease of the poliomyelitic type in children (Howitt, et al (32)). Nevertheless, Howitt (33) later stated he had made a mistake because he failed to inactivate the sera at 56°C. for half an hour in the serum neutralization tests, and he called attention to the need for destroying the aspecific factor changing with temperature change by heating it before going on to assay the neutralizing antibodies.

Newcastle disease virus has been held responsible for epidemic parotitis. A certain amount of anti-Newcastle disease antibodies has been found in the serum of patients affected by this disease. It should be recalled in any case that Jungherr, et al (40), on finding Newcastle disease virus serum-neutralizing indices in human blood in excess of 1,000, brought out that the presence of such antibodies in human blood serum does not indicate without any doubt that such persons have been infected with Newcastle disease virus. They therefore conclude that diagnosis of Newcastle disease in man must be made with due caution in isolating the virus in a patient.

Evans (23) noted that the presence of hemagglutination inhibiting antibodies is not strictly associated with the appearance of any particular set of symptoms, and can occur even in subjects who have never come in contact with the virus. In addition (24), he stated that about 50 percent of the sera taken from a group of laboratory workers were able to neutralize 10,000 ID₅₀ of the virus.

Howitt, et al (32) examined not only the sera of children with poliomyelitis type symptoms and of adults with influenzal symptoms as previously mentioned, but also the sera of subjects having no previous cases of such diseases in their medical histories. Neutralization tests carried out with such sera proved positive in 90 percent of the cases.

Cordier, et al (20) also noted that the sera of normal subjects showed hemagglutination inhibiting assays of from 1:40 to 1:80.

Collier, et al (19) in a similar investigation examining 1,182 sera, obtained the following results:

- 50.3 percent failed to inhibit in 1:10 dilution
- 24.7 percent inhibited hemagglutination in 1:10 dil.
- 15.6 percent inhibited hemagglutination in 1:20 dil.
- 5.8 percent inhibited hemagglutination in 1:40 dil.
- 3.6 percent inhibited hemagglutination in 1:80 dil.

Scatozza (67) studied antibodies for their ability to inhibit and complement fixate Newcastle disease virus in 1,363 samples of human serum. Since only 13 samples gave positive results, the author believes that Newcastle disease occurs rather rarely in man.

There is no doubt though that the most widely described clinical picture and the condition most readily found in man is one of conjunctivitis. Many cases have been reported in the literature, but certainly

others no less in number have been discovered and not described. Bona-duce (9), for example, tells me that he has observed it to occur in ten or so times. It hardly need be said that Newcastle disease conjunctivitis is found among those who have come in contact with Newcastle disease virus. In fact, the 33 cases mentioned in one set of statistics are distributed thus: laboratory personnel, 9; chicken-raising personnel, 19; chicken feed salesman, 1; fried chicken vendors, 1; veterinary students, 1; unknown, 2.

Localization of the Newcastle disease virus in the eye has been noted not only in man but also in various species of animals as appears from the literature consulted, which, for purposes of completeness I extended to cover all of the viruses in the so-called plague group to which the pseudo-plague or Newcastle disease virus belongs.

Ostertag, et al (59) observed that certain strains of plague virus can infect adult geese inoculated by way of the conjunctiva.

According to Hertel (31), Kleine, et al (43), the plague virus can penetrate into the body also by way of the conjunctiva.

Meloni (51) often observed also "hyperemia of the iris which appears either spotted or uniformly reddened" in the acute form of plague.

By infecting two chickens, one by conjunctival instillation and the other by rubbing a curved instrument coated with plague-infected blood against the cornea, he noted that the former survived while the latter died; as to the distribution of the virus in the various parts of the body, he also found the aqueous humor to be virulent.

Kleine (44) also found the virus in the cornea in chickens which died of the plague; furthermore, in a chicken infected with plague he observed atrophic foci at the rear of the eye, and in geese he found blue-gray chorioretinal foci.

Halasz (30) observed detachment of the retina in pigeons.

Stubbs (75) reproduced the plague infection in chickens by way of their eyes.

Nakamura, et al (55) reproduced the infection in pigeons by instillation in the conjunctival cul-de-sac of a drop of cerebral suspension of pigeons dead of the plague; on investigation of the distribution of the virus in the various organs, none was found in the cornea.

Doyle (22) saw that Newcastle disease virus infects animals sensitive to it when inoculated by way of the conjunctiva.

Serra (71) and Bisanti (8) admit the irregularity of infection with Newcastle disease virus extracted from the organs of infected animals when inoculated by way of the eye.

Moine (53) observed conjunctivitis and keratitis in Newcastle disease.

Dr. Izzo (36) observed cases of blindness in some of the chickens in his pens infected with Newcastle disease.

Clark, et al (17) observed that the aqueous humor of the eyes of chickens infected with Newcastle disease agglutinate blood corpuscles, and that this method is valid as a way of discovering the presence of the disease in its initial stages before hemagglutination-inhibiting antibodies appear in the blood serum.

In subsequent research carried out on chickens vaccinated and showing no signs of the disease, Clark, et al (18) became convinced that the aqueous humor is a reserve of the virus since they obtained considerably large hemagglutination percentages with isolation of the virus. Nevertheless, Dardiri, et al (21) hold that the aqueous humor of the chicken is not a reserve source for the virus.

Bonaduce has carried out interesting research in chicken (66), dog (11) and rabbit (10) eyes.

With respect to dogs, Bonaduce (11) observed that animals inoculated subcutaneously, intravenously or fed with Newcastle disease virus showed no clinical manifestations, whatever, nor was there any increase in hemagglutination-inhibiting antibodies. In addition, he failed to re-isolate the virus from the blood. Dogs inoculated with the same virus in the conjunctival sac show acute conjunctivitis, while those inoculated in the anterior chamber of the eye show cases of acute symptoms of glaucoma. After 12 hours, the animals show intense turbidity of the aqueous humor and infection of the conjunctiva (the virus contaminating the conjunctiva during manipulation). After 24 hours, there is intolerance of light, intense chemosis of the lower eyelid, the presence of conjunctival mucopurulent drainage, increased conjunctival infection, mydriasis, and a considerable endo-ocular hypertension.

These symptoms remain stationary for four days, after which they gradually recede, and by the twelfth day the animal is completely recovered.

It was possible to re-isolate the virus from the conjunctival sac wash fluid but not from the blood. A conspicuously high level of hemagglutination-inhibiting antibodies was demonstrated in the sera of the animals in this group.

With respect to the chickens (66), Bonaduce was able to discover that the virus inoculated into the eye induces conjunctival hyperemia after 12 hours; after 24 hours, the conjunctiva are redder and more swollen, particularly at the lower corner. These phenomena increase on the second day to the point that the eye opening becomes greatly impeded.

In cases with greatly accentuated edema, the conjunctiva appear covered with fibrinoid exudate and are bleeding.

Tissue studies show abundant exudation, predominantly lymphocytic, immediately beneath the epithelial covering, which is no longer recognizable: the conjunctiva are very much increased in thickness. A great number of hematic elements are also present among the elements of infiltration extending downwards and dissociating the elements in the muscular layer. There is no other appreciable change with respect to the eyeballs.

The virus inoculated into the previously emptied anterior chamber of the eye induces a perikeratic intrusion which increases until it becomes intense after 24-36 hours. There is also congestion of the iris, turbidity of the aqueous humor, the presence of exudate in the anterior chamber and on the front surface of the iris; in one case at the point of inoculation at the limbus, a corneal infiltration appeared surrounded by a zone of intense hyperemia; a focus of infiltration also appeared in the central area of the posterior surface of the cornea spreading to the greater part of this membrane.

The virus on being inoculated into the vitreous chamber brings about changes in the front portion of the eye less marked than those described above, while an exudation appears early in the vitreous chamber preventing one from observing the fundus oculi. After 36-48 hours, there could be an appearance of exudate in the area of the papilla; the iris also shows itself considerably congested at the same time.

Tissue analyses show in addition to the exudate in the vitreous cavity that lymphocytic infiltration frequently takes place, both in connection with the ciliary process and in the field of retinal tissue; the latter loses its normal structure at a number of points, being replaced by an infiltration tissue and by necrotic zones.

There is a moderate increase in the infiltration cells in the optic nerves of inoculated animals along the nerve fiber bundles; this was found to occur almost always and was most evident near the intraocular tumefaction of the optic nerve of the inoculated eye.

The animals infected by the routes as above never showed any lesions to the uninfected eye except in one case. Animals experimentally infected (subcutaneously) or diseased by natural causes never showed any lesions of the eyes.

Virus inoculated by the ocular route and subcutaneously can be re-isolated after 48 hours in all cases from the blood, from the aqueous humor of the eye that was not treated, and from the brain. Nevertheless, the question of the direct passage of the virus from the inoculated eye to the other one does not seem to find any positive answer in this investigation. As a result, it would seem wiser to adopt the hypothesis that

the fact would be a consequence of the spreading of the virus throughout the organic tissues and fluids.

In rabbits, though, Bonaduce (10) carried out investigations to study the behavior of hemagglutination-inhibiting antibodies following inoculation with Newcastle disease virus in the anterior chamber of the eye and intravenously.

The results attained show that rabbits, though showing no clinical symptoms whatever, react each time with the formation of a considerable amount of antibodies in the blood. They also show that inoculation of the virus into the anterior chamber of the eye leads to the formation of antibodies also in the aqueous humor of the inoculated eye, but not in the other eye. On the other hand, those animals which were inoculated intravenously do not show any presence of antibodies in the aqueous humor. These facts would indicate that the presence of antibodies in the aqueous humor was due to local infection.

Bozzo, et al (13) observed that the Newcastle disease virus, on being inoculated into the anterior chamber or into the layers of the cornea in rabbits, brought about an appreciable change in the eye tissues' response to re-inoculation of the anterior chamber with the same virus, reducing or inhibiting the formation of the lesions induced by such virus. This modified reactivity of rabbit eye tissues towards the virus's toxic action was observed to occur both 21 days after the first inoculation and just a few hours after the first inoculation. The resistance to the toxic action of the virus 21 days after the first inoculation should be interpreted as an expression of a state of antitoxic immunity which came into being as a result of the first inoculation with the virus. The mechanism whereby the early antitoxic immunity is established remains unclear.

Conjunctivitis due to Newcastle disease in man was described for the first time in 1943 by Burnet (15), and was then announced by many other investigators (Yatom (79), Anderson (1), Shimkin (71), Radnot (64), Kujumgiev (45), Freyman, et al (26), Ingalls et al (35), Jacotot et al (37), Lepine et al (41), Beaudette (5), Gustafson et al (29), Borsello et al (12), Latte et al (46), (47), Tapolnik et al (76), Berke et al (6), Sinkovitz (73), Kyle et al (42), Wagner (78), Pomeroy (61), Moolten et al (54), Mitchell et al (52), Bieling et al (7), Schoop (69), Quinn et al (63), Placidi et al (60), Hunter et al (57), Jeldon (39), Lippman (49), Slonim et al (74), etc.). The infection is due to direct or indirect contact between the conjunctive and contaminated hands or by way of infected material which flies into the eyes.

The incubation period varies from more often a few hours to more rarely two to three days. As a rule it attacks only one side.

The disease symptoms affect primarily the eye, but sometimes general symptoms of illness, chills, headache, back pains and fever can occur.

Subjective symptoms include itching, lacrimation, the feeling of a foreign body or intolerance of light. Objectively one finds a more or less marked edema of the eyelids sometimes extending to the cheek, edematous hyperemic conjunctivitis and sometimes bleeding, but generally to no large extent. It is possible to find a moderate hypertrophy of the papilla and the development of follicles, particularly on the part of the lower conjunctival fornix. The nictitating membrane is highly swollen and hyperemic in some cases; the bulbar conjunctiva can be affected in different ways, showing chemosis or being only moderately hyperemic. Keeney, et al (41) found in one case that the cornea had been affected in the form of small, pinpoint epithelial infiltrations revealed by fluorescein.

The secretion which is at times abundant is of catarrhal type; at other times it is somewhat scarce and is primarily lacrimal.

There is almost always a regional lymphadenitis with swelling and painfulness of the preauricular lymph glands.

An examination of conjunctival smears brings out the presence of leukocytes (mostly neutrophilic and lymphocytic), with some red blood cells and fibrin. The observation made by Keeney, et al (41), (34), is interesting in this respect as they are said to have observed epithelial cell cytoplasmic inclusions in conjunctival smears. These authors, having made smears from the lower cul-de-sac of the affected eye and staining them with Giemsa's stain, found before fixing them in dehydrated alcohol that the conjunctival epithelial cells contained small granular, cytoplasmic inclusions varying in coloration from burgundy red to purplish blue.

Attempts to reproduce such cytoplasmic inclusions in the conjunctiva of rabbits, in chorioallantoic membranes, in the meninges of the embryos of infected chickens failed to succeed. These inclusions were not found by Latte et al (46), (47) in five volunteers who were infected with Newcastle disease virus, nor could Orlandella (58) discover them in two persons infected by natural causes.

Moderate leukopenia accompanied by relative leukocytosis may occur in the blood.

The illness has a duration of ten or so days: the final outcome has always been satisfactory, and no cases of complications have ever been reported.

Relapse or recurrence is possible. Jacotot, et al (38) report that a laboratory worker was reinfected four years and eight months later. This second infection manifested itself like the first with an acute conjunctivitis accompanied by mild general disturbances, but with an angina added to it. In addition, unlike the first time, the serum did not show any antibody activity.

Differential Diagnosis

The following two groups of inflammations can be taken into consideration for diagnosing conjunctivitis resulting from Newcastle disease virus:

a. An acute catarrhal conjunctivitis arising from *Diplococcus pneumoniae*, *Staphylococcus pyogenes* var. *aureus*, *Hemophilus influenzae*, etc.

The initial symptoms are similar, but in these cases the systemic indications are absent, and the discharge is much more profuse and mucopurulent. Smears can show a preponderance of neutrophilic granulocytes and usually the bacteria causing the disease.

b. An acute follicular conjunctivitis such as the conjunctivitis with inclusion bodies in adults, Beal's conjunctivitis and epidemic keratoconjunctivitis.

These diseases are more follicular since the subepithelium shows a lymphocytic response, while in Newcastle disease there is a more pronounced papillary or primary vascular response.

1. In Beal's conjunctivitis, the similar course of the illness and the secretion can lead to confusion in diagnosis, but usually the intense concentration of follicles and the complete sparing of the cornea aid in the diagnosis. The virus has not been isolated in cases of this disease, and according to Thygeson (77) attempts to transmit the disease to laboratory animals have proven unsuccessful.

2. Inclusion conjunctivitis in adults (paratrachoma) can lead to confusion of the cytoplasmic inclusions with those occurring in the case of Newcastle disease, but here the symptoms are usually serious. The discharge is purulent and contains many segmented granulocytes. Both the acute stage and the period of convalescence last longer than in Newcastle disease.

3. In keratoconjunctivitis, the secretions are similar to those in Newcastle disease, but the development of pseudo-membranes, intranuclear inclusions and corneal infiltrations of more marked appearance together with the impaired vision make the diagnosis clear.

Keeney, et al (41) believe that "many cases diagnosed as superficial punctate keratitis can now be attributed to infection by Newcastle disease virus. Similarly the disease described by Patton and Gifford [Translator's Note: Probably Gifford (Harold Gifford, American oculist, 1858-1929)] in 1921 as agricultural conjunctivitis in the American farming districts could be caused in some cases by diseased poultry."

With respect to choosing between a diagnosis of Newcastle disease conjunctivitis and Beal's type of follicular conjunctivitis, it should

be added that the distinction between the two diseases pointing to more prolific development of follicles or the absence of corneal lesions in Beal's form does not seem to Latte, et al (46) too valid for establishing a differential diagnosis. In fact the development of follicles can take place in different ways in Newcastle disease according to the case involved. These authors found that there was an extremely marked follicular hypertrophy in one of their cases, it being the only outstanding feature in the general clinical picture.

It should be noted with regard to the corneal lesions that they are absent in Newcastle disease conjunctivitis, and have only been found by Keeney, et al (loc. cit.).

The presence of small hemorrhages in certain cases of Newcastle disease conjunctivitis, an event which is said never to occur in Beal's conjunctivitis, can only be made use of in those cases where it does occur.

The fact that no virus can be found present in cases of Beal's conjunctivitis (Thygeson) appears to be a more consistent basis for diagnosis.

Diagnosis

Leaving apart the changes in the histiocyte picture, too aspecific to have any diagnostic use, and the cytoplasmic inclusions described by Keeney, et al (loc. cit.), not observed by other authors [Latte, et al (loc. cit.), Orlandella (loc. cit.)], the following factors are based on more dependable criteria for diagnosing Newcastle disease in man: past medical history, isolation of the virus from conjunctival secretions, appearance of the antibody in the circulation.

The patient's past medical history can tell whether his eye has ever been in contact with material containing Newcastle disease virus.

One can only be certain though by carrying out laboratory tests, but even then with due reservations as will be pointed out.

To isolate the virus, one first washes the patient's eye with sterile physiological solution. These washings are then treated with antibiotics and are inoculated into 11-day-old chicken embryos. Between 30 and 48 hours later the amniotic-allantoic fluid is removed from those eggs whose embryos have died showing the well-known lesions induced by the action of Newcastle disease virus (velvety, thickened, hemorrhagic M.C.A. [Translator's Note: abbreviation not explained in text. C.A. means anterior chamber of the eye.]; embryos with diffuse pinpoint hemorrhages). One then tests these fluids for absence of bacteria. They must have a hemagglutinating action which is an index of the presence of the virus. The virus's Newcastle disease nature will be determined by means of an anti-Newcastle disease virus immune serum's inhibition of hemagglutination or serum neutralization. On the other hand, one can

determine the extent to which these fluids induce disease in chickens.

As to serological tests, one can resort to assaying the hemagglutination inhibiting antibodies, the complement fixing antibodies and the neutralizing antibodies in the patient's serum, taking care to inactivate the sera at 56°C. for half an hour to destroy any aspecific factors present also in normal sera which could falsify the results.

In this respect, one need only remember what happened to Howitt, et al (loc. cit.) as previously mentioned.

It is still important to note that sometimes negative results may be obtained; in such cases the failure to isolate the virus and the failure to demonstrate any presence of antibodies specific for Newcastle disease virus in the circulation or, rather, the failure to show any significant rise in their level, does not exclude the fact that the eye infection may have been due to Newcastle disease virus.

Every caution should be taken before coming to the conclusion that the illness is not caused by Newcastle disease virus due to the transitory positiveness of conjunctival secretion cultures in embryonated eggs which may come to a stop, as Latte, et al (loc. cit.) have noted to happen even on the second day in experimentally-induced disease, as well as due to the absence of serological indications such as has been found by a number of authors, for example, Latte, et al (loc. cit.) in two patients out of five who were infected experimentally even though it was certain that they were already infected with Newcastle disease.

Treatment

Newcastle disease conjunctivitis runs a benign course since it cures itself spontaneously in ten days or so, but treatment of its symptoms does serve a purpose as it may prevent any complications.

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